BRONCHO-PULMONARY ASPERGILLOSIS*

A REVIEW AND A REPORT OF EIGHT NEW CASES

BY

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The fungus *Aspergillus* is sometimes found in patients suffering from certain chronic lung diseases such as tuberculosis. In these patients it does not alter the clinical or the pathological picture to any material extent and causes merely a harmless secondary or saprophytic infection. In some reports aspergillosis, often on scanty evidence, is claimed to be a primary infection presenting as bronchitis, pneumonia, lung abscess, or multiple granulomata.

In this paper the literature is reviewed and eight new cases are reported, including three of a kind not previously recognized; the clinical manifestations of this type of aspergillosis are discussed in detail. The three cases resemble to some extent the condition recently described under the term " pulmonary eosinophilia." Evidence is offered that in our patients sensitization of the host to infection by this fungus led to pathological changes which warrant a description of the condition as a true broncho-pulmonary aspergillosis, whether the fungal infection was implanted on a pre-existing lesion or not.

MYCOLOGY

The genus of moulds, *Aspergillus*, was first described and named by Micheli (1729). The similarity in appearance between its fruiting heads and the brush used for sprinkling holy water (*aspergillum*) probably suggested the name. This fungus is very commonly found in soil and decaying organic matter (Thom and Raper, 1945). It is present in compost heaps, proprietary hop manures, spoiled grain, hay, and straw, and also in rotting wood. The ubiquity of its spores is responsible for frequent contamination of laboratory cultures, and therefore the diagnosis of aspergillosis should not rest solely on cultural findings.

This fungus can be grown on simple media. Originally we used Sabouraud's (1894) maltose agar to which sterile horse or human blood was

added immediately before use. However, good growth occurs on ordinary blood agar plates and we have abandoned the use of the special media for the primary isolation. The plates are inoculated in duplicate and incubated at 37° C. Colonies will be produced at incubation temperatures up to 45° C., a property which might be of value in producing pure cultures. If, however, repeated subcultures are made on media containing penicillin and streptomycin, to which our strains are insensitive, colonies free from bacterial contamination are obtained and these are suitable for animal experiments.

A colony of aspergillus has a basal white felt consisting of an interwoven mycelium of septate hyphae. Occasional cells of the hyphae enlarge and are then known as foot cells. A foot cell gives off a shoot which, elongating upwards, is known as a conidiophore and bears at its free extremity a swollen vesicle. From this vesicle shorter stalks (phialides) arise like the bristles of a brush and each stalk bears a row of conidia or spores, which may be coloured and give the varying tints of the mature colonies.

The following groups of the fungus are described as pathogenic to man: *A. fumigatus, A. niger, A. clavatus, A. versicolor*. Of these *A. fumigatus* is the commonest and was found in all of our cases in which final identification was possible. Rough separation into these groups may be made on morphological grounds. For example, *A. fumigatus* has a flask-shaped vesicle with a single row of phialides over its upper two-thirds only. *A. niger* has a spherical vesicle with one row of metulae borne over the whole surface from which phialides arise (Fig. 1).

A. fumigatus is a common pathogen of birds. Our strains, when inoculated intravenously into domestic hens, caused death in four to five days with multiple small granulomatous lesions containing the fungus in the lungs, liver, and spleen. It is also pathogenic to rabbits, and one of our strains which was given intravenously caused

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A. CONIDIA   B. PHIALIDES   C. METULAE   D. VESICLE
E. CONIDIOPHORE
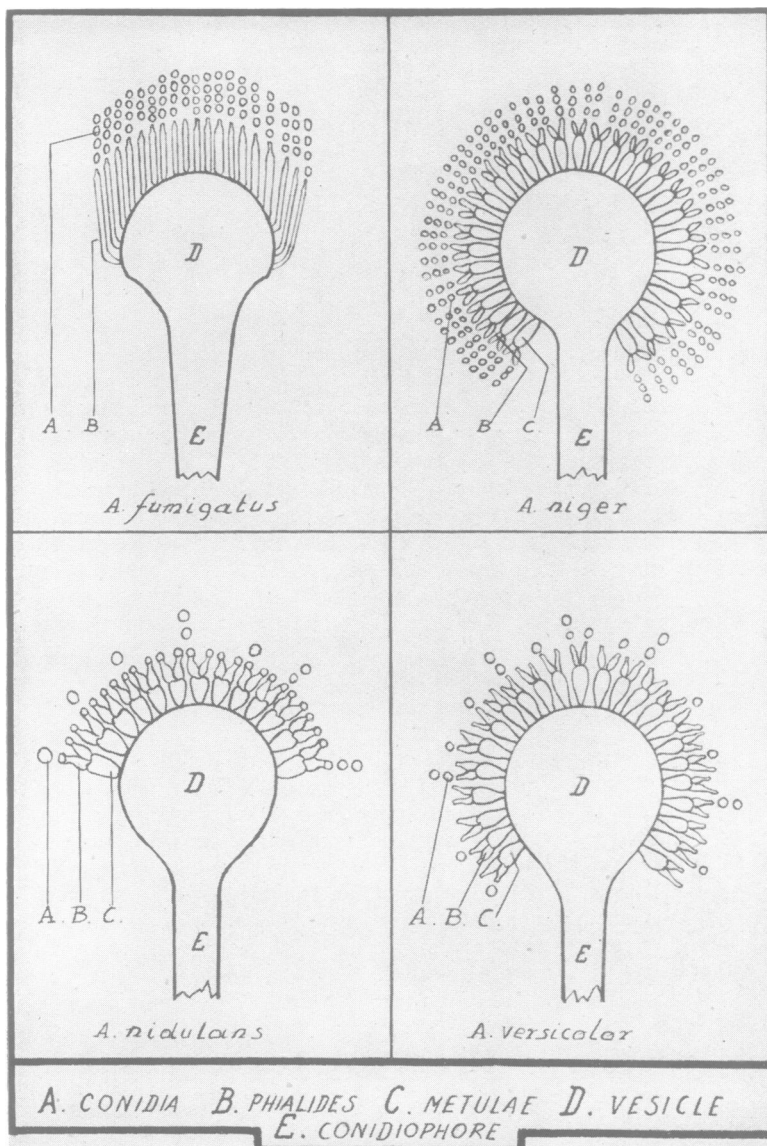
FIG. 1.—Diagram showing morphological differences between strains of the fungus *Aspergillus*.

heads in their sections it is possible that there was confusion between hyphae cut in transverse section and conidia. In our animal experiments, vesicles, phialides, and conidia were not observed.

In sputum and bronchial aspirations we have seen only the mycelium and never the fruiting heads of the fungus. In such specimens the mycelium occurs in white or brownish flecks which are just visible to the naked eye. These flecks may be examined microscopically as wet unstained films or the specimen may be cleared by a drop of liquor potassae. If a permanent preparation is required the film should be fixed with Schaudinn's solution and stained with haematoxylin and eosin. In some of our cases these mycelial flecks are aggregated together with mucus, fibrin, eosinophils, Curschmann's spirals, and Charcot-Leyden crystals into rounded, brown, dull granular masses about one centimetre in diameter which stand out from the rest of the specimen. These we refer to as " plugs " ; they differ from the coiled masses of fibrinous or plastic bronchitis in their colour and matt opacity (Fig. 2).

Microscopically these plugs are similar to the material removed at bronchoscopy from one of our cases. Under the low powers the sections show amorphous pale-staining eosinophilic material separated into layers by thin zones of inflammatory and desquamated epithelial cells (Fig. 3). With higher magnifications the eosinophilic material is seen to consist of fibrin strands, Curschmann's spirals, and Charcot–Leyden crystals. The mycelium can be demonstrated by the appropriate stains (Fig. 4). The bronchial mucosa in the biopsy material shows only mild inflammatory changes, although the mycelium is
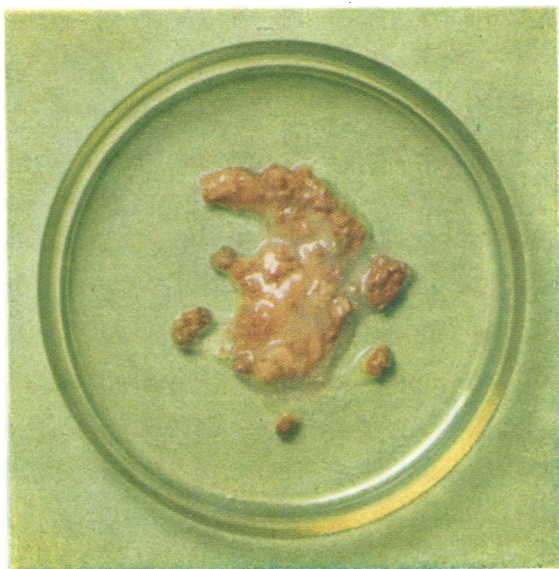
death in seven days with multiple granulomata in the lungs and kidneys. Attempts to infect guinea-pigs intramuscularly were unsuccessful, and the fungus failed to grow after inoculation into artificial haematomata in guinea-pigs.

The lesions described by Hertzog, Smith, and Goblin (1949) in the lungs of a child who died with multiple granulomata appear to be similar to those observed in our animals. An illustration in their article bears the legend " hyphae and spores," but as they do not mention the appearance of fruiting

FIG. 2.—A sputum plug from Case 7 separated for display.

hardly that of an inflammatory response but of an allergic exudate which contains the mycelium and is bound together by fibrin and so forms a mechanical obstruction.

The demonstration of the fungus in histological sections is more difficult. The mycelium is cut into short, isolated fragments which have to be identified in the midst of mucus-containing exudate. After formalin fixation the mycelium is poorly stained by haematoxylin and may not be distinguished in the eosinophilic debris ; the periodic-acid-magenta method is an excellent stain for mucus and so is not suitable for sections of

FIG. 4.—Biopsy specimen of Case 6 (× 300) showing silver impregnation of hyphae within the bronchial exudate.

present in the crypts of the mucous glands. We were unable to demonstrate the fungus in the sub-mucosa.

It is probable that the plugs are expectorated portions of the masses that have been seen bronchoscopically to be blocking bronchi and producing the radiological picture of collapse and consolidation. In one operation specimen the material occluding the bronchus was exactly similar histologically to the plugs and to the biopsy material from the other cases. The picture is
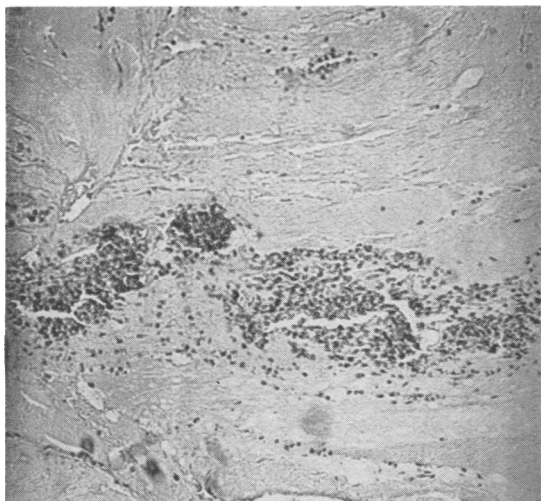
bronchial exudate. If the preparation is treated by Robb-Smith's modification of Foot's reticulum stain we find that the hyphae are strongly impregnated with silver and stand out well against the yellow mucus. This has been the method most commonly used in our cases.

All stages in the development of the fungal colony may be seen in a lung infarct (Fig. 5). Mycelial masses are present within the bronchi, the alveoli, and even invading the thrombosed vessels. Within the alveoli the hyphae, fruiting heads, and spores are clearly seen. In our case it appeared that invasion was limited to the periphery of the infarct, and it may be conjectured that in this site the conditions are suitable for optimal growth.

The strains which we have isolated have been insensitive to penicillin, streptomycin, chloramphenicol, and aureomycin, both singly and in combination. It was also found that the cultures were unaffected by the common sulphonamides. We
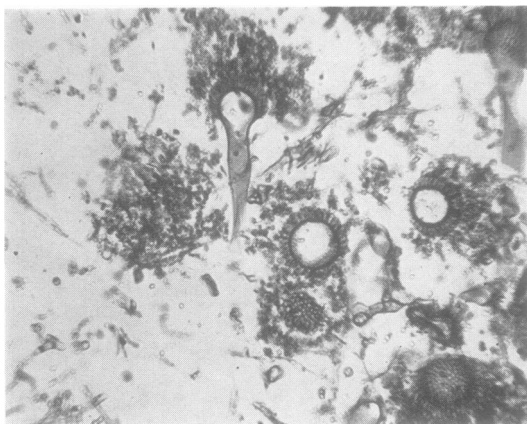

FIG. 3.—Biopsy specimen of Case 6. Inspissated mucus separated by layers of fibrin and some inflammatory cells. (H. and B., × 70.)

FIG. 5.—Photomicrograph of section from Case 1 (Masson, × 200) showing hyphae, fruiting heads, and spores within a lung infarct.

are indebted to Dr. F. C. O. Valentine of the London Hospital for showing that they were sensitive to 4:4 diamidine-diphenylamine dihydrochloride (M and B 938) in dilutions of 1 in 100,000. Major H. A. Dade, of the Commonwealth Mycological Institute at Kew, kindly supplied 16 other strains of *A. fumigatus* isolated from various human, bovine, avian, and vegetable sources. Their sensitivity to these drugs and antibiotics was similar.

HISTORICAL REVIEW

The first reference to the invasion of animals by the fungus was by Mayer (1815), who observed it in the lungs of a jay. Subsequently it was found in other birds by Jägar (1816), Heusinger (1826), Deslongchamp (1841), and Robin (1853), and in a laryngeal swelling in a horse by Rivolta (1887).

The first reference to a human invasion by the aspergillus is usually attributed to Hughes Bennett (1842), but he himself thought the infecting agent was a penicillium, and his description and the figures given are not those of an aspergillus. Rayer (1842) reported a similar case, and Küchenmeister (1855) found a fungus infection in a man with cancer of the lung.

The first human case in which the aspergillus was definitely identified was described by Sluyter (1847) in a woman dying of an unspecified pulmonary infection. Subsequently Virchow (1856) described four cases of a pulmonary aspergillus infection in patients dying of other conditions. Friedreich (1856) and Fürbringer (1876) reported the finding of the fungus growing in tuberculous cavities. Cohnheim (1865) recognized it in the alveoli of a man with pulmonary infarction and Lichtheim (1882) reported a similar case.

Osler (1887) reported the case of a woman aged 29, who, for 11 years at roughly three-monthly intervals, had coughed up dark bodies, the size of a bean, which consisted almost entirely of the mycelium and spores of an aspergillus. Young (1926) reported another case in which a man coughed up a body the size of an almond and consisting of fibrous tissue from the centre of which *A. fumigatus* was grown. No source of the fungus was found at necropsy.

The first reference in the English literature was by Wheaton (1890), who found aspergillus in the lungs and lymph nodes of a child aged 2 years who died of pneumonia.

Dieulafoy, Chantemesse, and Widal (1890) were the first to describe the disease in pigeon-crammers and they called it *maladie des gaveurs*. The pigeon-crammers of Paris performed " gavage " by taking a mouthful of grain and water and spitting it into the mouth of a pigeon. Each man fed about 2,000 pigeons a day and it was well known among them that they would succumb to a chronic pulmonary disease. Rénon (1893, 1895, 1897) amplified these findings and also reported two new cases in hair-combers who used rye-flour for removing grease from hair before making it into wigs. He also referred to primary and secondary aspergillosis, including in the latter category those cases in which the fungus was found in association with carcinoma, bronchopneumonia, or tuberculosis. As his evidence for the existence of a primary form he cited his failure to find tubercle bacilli in most of his cases and also the results of his animal experiments in which rabbits and pigeons died 10 to 20 days after inoculation with *A. fumigatus*. He also failed to find aspergillus in the sputum of numerous control subjects. His cases were, unfortunately, not supported by any post-mortem evidence.

Boyce (1892) and Arkle and Hinds (1896) reported two further English cases, the former in association with thrombosed vessels.

Mirsky (1903) first reported finding *A. versicolor* in the sputum and Steele (1926) reported a similar case. *A. nidulans* was found in the sputum by Holden (1915), *A. niger* by Bethune and Moffatt (1933), Cannon (1935), and Hetherington (1943), and *A. flavus* by Wahl (1928).

Raether (1912) stated that man was relatively immune to aspergillus infections and that a large infecting dose was necessary. Grippe and diabetes, according to Kleberger (1920) and Kaufmann (1922), might be predisposing causes of pulmonary aspergillosis.

A case of aspergillus infection of the pleural cavity following an empyema due to a gunshot wound was described by Cleland (1924).

Rénon (1897) was the first to mention the occurrence of asthma in aspergillosis and it was not mentioned again until van Leeuwen, Bien, Kremer, and Varekamp (1925) drew attention to the association of the two conditions. Subsequently several authors, Hansen (1928), Bernton (1930), Flood (1931), Brown (1932 and 1936), and Feinberg (1936), showed that between 1 and 20% of asthmatics gave positive skin tests to extracts of aspergillus.

Castellani and Chalmers (1919) in a general review of the fungus said that *A. fumigatus* was the commonest type found and that this was usually a saprophyte but that it might rarely cause a " pseudo-tuberculosis." Castellani (1927 and 1928) stated that the diagnosis of aspergillosis could be made by finding the organism in the sputum. At necropsy in one case there were numerous mycotic nodules in the lungs, liver, and kidneys, but he failed to find fruiting heads in the tissues. Many other authors have reported cases in which the diagnosis of aspergillosis appears to have been made on the evidence of sputum findings (Paradice, 1924 ; Steele, 1926 ; Lapham, 1926 ; Wahl, 1928 ; Schneider, 1930 ; Peutz, 1932 ; Bethune and Moffatt, 1933 ; Smith, 1934 ; Penta, 1935 ; Cannon, 1935 ; Edwards, 1935 ; Fawcitt, 1936 and 1938 ; Moolten, 1938 ; Stolow, 1939 ; Vadala, 1940 ; Van Ordstrand, 1940 ; Donaldson, Koerth, and McCorkle, 1942 ; Delikat and Dyke, 1945 ; Coe, 1945).

Hertzog and others (1949) reported a case of " acute fulminating aspergillar pneumonia " in the 5-year-old son of a farmer. An acute respiratory infection developed fairly rapidly, the boy being cyanosed, dyspnoeic, and pyrexial. Radiography showed diffuse bilateral pulmonary infiltration which was thought to be consistent with pulmonary tuberculosis. Culture of a throat swab grew no fungus and there was no eosinophilia. The boy died within 24 hours of admission to hospital, and at necropsy discrete and confluent, greyish-white nodules were seen scattered throughout both lungs. Histological examination showed a widespread patchy granulomatous process, with tubercles which were composed of a centre of neutrophils and a peripheral zone of epithelioid cells and large multinucleate giant cells. *Myco. tuberculosis* was not found after guinea-pig inoculation. Numerous large hyphae and spores were seen, and on culture *A. fumigatus*, but no other organism, was grown. Cawley (1947) reported multiple mycotic abscesses

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due to *A. fumigatus* in the lungs of a child at necropsy, and Cooper (1946) and Duncan (1945) found similar abscesses in adults.

Several authors (Sayers and Meriwether, 1932 ; Fawcitt, 1938 ; Twining and Kerley, 1951) referred to the fine mottling in radiographs of the chest in pulmonary aspergillosis. Van Ordstrand (1940) mentioned a shadow radiating from the hilum, which he called the " sun-burst " radiographic appearance. Hemphill (1946), Gerstl, Weidman, and Newmann (1948), and Twining and Kerley (1951) described the radiological appearance of a large ovoid cavity, with a thick wall containing within it a mobile mass ; they called this a " mycetoma."

The results of animal experiments were first reported by Rénon (1897) and Dieulafoy (1912) ; they found that inoculation with *A. fumigatus* caused the death of pigeons in three to four days, rabbits in six to eight days, and guinea-pigs in four to five days. Lapenta (1921) described similar findings. Bethune and Moffatt (1933) found that experimental intratracheal injection or inhalation of *A. niger* into rabbits did not produce any permanent lesion, nor did it worsen the prognosis of tuberculous animals. Henrici (1939) prepared a toxic " cell-sap " from *A. fumigatus*. After centrifuging and Seitz filtration this fluid was found to be lethal to rabbits, guinea-pigs, and chickens ; rabbits were actively immunized against it. The chemical nature of this cell-sap was not discovered, but precipitation experiments suggested that it was not a protein or a polysaccharide.

CASE REPORTS

CASE 1.—J. C., a man aged 31 years, had always been a French-polisher in a furniture factory.

He had suffered from severe bronchitis all his life with copious purulent sputum. In 1948 he was admitted to hospital suffering from cor pulmonale. Bronchograms showed generalized bronchiectasis.

After an intravenous injection he developed thrombophlebitis in his left arm. A pulmonary embolism led to his death three days later.

Necropsy.—There were signs of chronic congestive heart failure. In the lungs there was recent infarction of the whole of the apical and posterior segments of the left upper lobe with a smaller infarct in the apex of the left lower lobe.

In sections of the infarct the fungus was found in the necrotic bronchi, bronchioles, alveolar spaces, and permeating the thrombi in the vessels. It appeared to be proliferating most freely just inside the necrotic area as though the optimal conditions of oxygenation and nutrition were limited to this zone. Together with the hyphae there were large numbers of fruiting heads with their spores (Fig. 5).

CASE 2.—E. F. B., a man aged 58 years, at the time of admission had been a stoker for one year. Before this, for 17 years, he had worked in stables in close contact with grain, hay, and manure. He also kept budgerigars.

In September, 1950, he coughed up 2 oz. of bright red blood. A radiograph showed a circular shadow at the left apex with a small clear zone surrounding it and another clear cyst at the right apex. Tomograms in October, 1950, and January, 1951, confirmed this appearance of a solid mass lying loose in a cavity (Figs. 6 and 7). On these films a diagnosis of "blood cyst" or "mycetoma" was made. He continued to have haemoptyses of up to 2 oz. intermittently until admitted to hospital in October, 1951. A. fumigatus was twice isolated from his sputum, but subsequently repeated examinations failed to demonstrate it. Tomograms in November, 1951, showed that the mass had increased in size and that the translucent area surrounding it was no longer apparent. The white blood count was normal, and there was no eosinophilia. On November 25, 1951, the apical segment of the left upper lobe was resected by Mr. J. R. Belcher.

Pathology.—At the apex of the lobe there was a circular plaque of thickened adherent pleura. The cut surface showed a spherical cyst 1 in. in diameter with a thin, white wall filled by brown, amorphous debris. Between this cyst and the pleural plaque were two much smaller cysts with similar contents (Fig. 8). Histologically the wall of the larger cyst was composed of fibrous tissue lined by an incom-

FIG. 7.—Case 2: 6-cm. tomogram to show a solid mass lying free in the cavity (31.1.51).

plete layer of ciliated columnar epithelium. In the smaller cysts the epithelial layer was complete. The solid contents of each cyst had an outer zone of blood and blood products, and within this was a mycelial mass in which fruiting heads were not present (Fig. 9).

This is a good example of the condition described as a "mycetoma" by Twining and Kerley (1951), and it is to be noted that the basic pathology in this and the following case is that

FIG. 6.—Case 2: a solid shadow at the left apex surrounded by a translucent area (September, 1950).
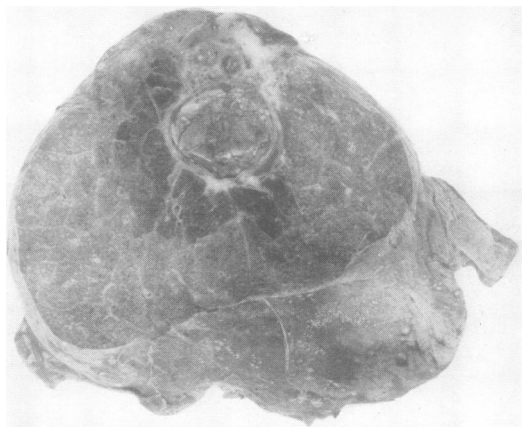

FIG. 8.—Case 2: Specimen showing a bronchiectatic cavity 1 in. in diameter filled with blood clot and mycelium. There are two smaller similar cysts above.

of a bronchiectatic cyst largely filled with altered blood and the fungus.

CASE 3.—C. T. W., a man aged 57 years, had been a gardener for 20 years. He was admitted to hospital because of recurrent haemoptyses, up to half a cupful in amount, for the previous 10 years, becoming more frequent recently. Radiography revealed an oval shadow in the right upper lobe of even density with a translucent area at the top. This was thought to be characteristic of a " blood cyst." After a right upper lobectomy by Mr. W. P. Cleland, he made a good recovery.

Histology.—The material received was a slice from a lobectomy specimen showing a cyst about 1½ in. in diameter. The cyst itself was lined with ciliated columnar epithelium beneath which was an extensive inflammatory exudate containing a fair number of eosinophils. The contents of the cyst were composed of layers of blood clot, desquamated epithelium, inflammatory cells with, towards the centre, a felted mass of mycelial elements. Vesicles and phialides were not present. Similar mycelial masses were present in some of the smaller dilated bronchi near the cyst. As mucous glands and plates of cartilage were present in the wall this represented a bronchiectatic cyst and was another example of a " mycetoma." Although there was no opportunity for cultural study to prove the identity of the fungus, morphologically it resembled an aspergillus.

CASE 4.—M. T., a woman aged 50 years, had been employed in asbestos and cardboard-box factories.

For the 10 years preceding admission she had suffered from recurrent attacks of bronchitis and pneumonia, with occasional small haemoptyses. On admission to hospital with an acute respiratory infection a radiograph showed thickening of the pleura lining the mediastinum, diaphragm, and lower part of the chest wall. There was bilateral upper zone fibrosis, more severe on the right than the left, with a suggestion of a cavity on the right. In spite of treatment with oxygen and antibiotic drugs she died two days after admission.

Necropsy.—In addition to the typical findings of congestive heart failure there was obliteration of the pleural space over the upper lobe. The cut surface of the lung showed the typical fibrosis of asbestosis together with a cavity in the upper lobe filled with dark brown debris (Fig. 10). Histologically the lining of the cavity consisted of granulation tissue passing into firm fibrosis containing carbon pigment and asbestosis bodies. There was no evidence of tuberculosis. Elements of a bronchial wall could not be
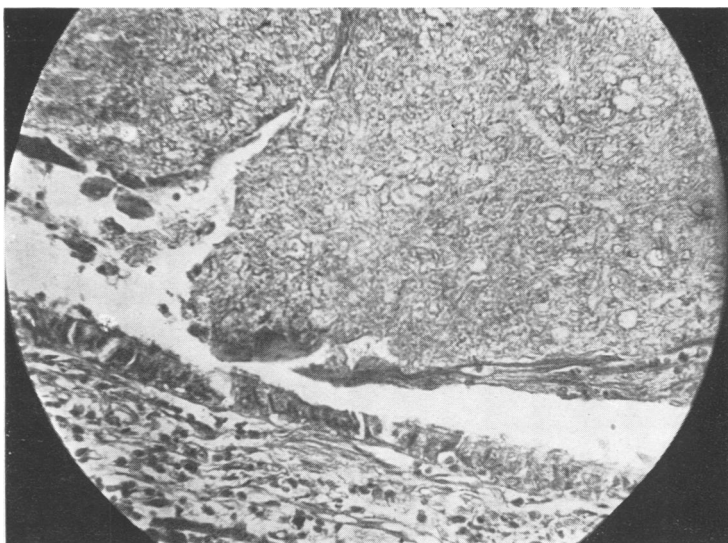
FIG. 9.—Mycelial mass within a bronchus lined by ciliated epithelium. (H. and B. × 300.)

identified within the gross fibrosis, but the contents of altered blood and mycelium were similar to those in Cases 2 and 3, and this may also be a " mycetoma." No cultures were made in this case.

The association of the fungus in these three cases with blood clot and its occurrence in infarcts suggested that blood or blood products might be necessary for the production of infection in resistant animals. Experimentally, as mentioned above, we failed to confirm this.

CASE 5.—M. G., a woman aged 31 years, was a shorthand typist and had no particular contact with birds, grain, or any vegetable matter.

She had suffered from bronchitis all her life. Three years b e f o r e admission bronchiectasis of the right lower and both upper lobes was diagnosed. Later it was considered t h a t a
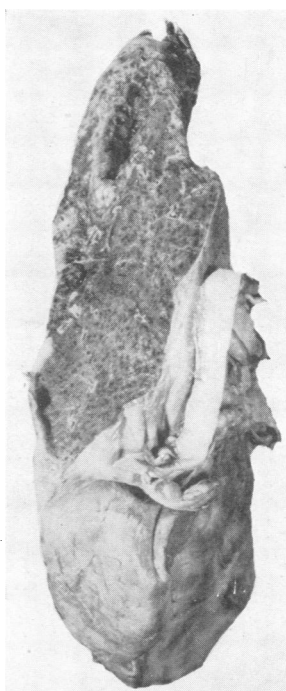
FIG. 10.—Case 4: post-mortem specimen of lung showing asbestosis with a cavity in the upper lobe.

right lower lobectomy would give symptomatic relief. On admission she had a severe cough producing 4 oz. of purulent sputum daily in which she had noticed no plugs. There was an absolute eosinophil count of 913 per c.mm. The right lower lobe, except for the apical segment, was resected.

Histology.—The lobectomy specimen showed bronchiectasis of the basal branches. The lumen of the anterior branch was filled by firm, laminated material, and the segment itself contained some small areas of collapse (Figs. 11 and 12). In sections the bronchus was lined with ciliated columnar epithelium and there was considerable inflammatory exudate, including many eosinophils in the submucosa. The mass occluding the bronchus was composed of mucus, fibrin, Curschmann's spirals, Charcot-Leyden crystals, and inflammatory cells. Suitable stains showed the mycelium of the fungus. Until the specimen was examined there had been no suspicion of aspergillosis, but the laminated appearance of the material in the affected bronchus was so similar to that in the bronchi of Case 8, in which a diagnosis had been made during life, that suitably stained preparations were made.

It should be noted that in the mycetomata (Cases 2, 3, and 4) the contents consist almost entirely of mycelium, whereas in this and the following cases hyphae are relatively scanty and the occluding material is composed of fibrin and inspissated mucus (Figs. 3 and 4).

CASE 6.—E. T., a woman aged 45 years, was a farmer's wife in the South of England, and among her other duties she handled and fed some hundreds of chickens.

There is no history of any allergic manifestation in her family.

In September, 1947, she gradually developed pain in the right side of the chest with cough and blood-stained sputum. Radiographs showed consolidation in the right upper lobe which cleared slowly without specific treatment, leaving some residual fibrosis (Figs. 13 and 14).

In July, 1949, she had a similar febrile illness, again with radiological evidence of consolidation in the right upper lobe. This responded slowly to penicillin therapy. In August the right upper lobe was almost clear, but there was collapse of the left lower lobe which persisted for nearly a year. She remained fairly well until November, 1949, when she had another febrile illness and was admitted to hospital for investigation (Figs. 15, 16, and 17). She had a cough with purulent sputum and was wheezy and dyspnoeic. There was an eosinophil count of 4,200 per c.mm.; in only one of many subsequent blood counts was the eosinophil count below 1,000 per c.mm.

Bronchoscopy in December, 1949, revealed a rounded tumour obstructing the left lower lobe bronchus. Histologically this mass consisted of polymorphonuclear and eosinophil leucocytes, desquamated epithelial cells, Curschmann's spirals, Charcot-Leyden crystals, and fibrin. The whole mass was infiltrated by the mycelium of a fungus which was also seen within a bronchial gland duct, but it did not appear to be invading the tissues (Figs. 3 and 4).
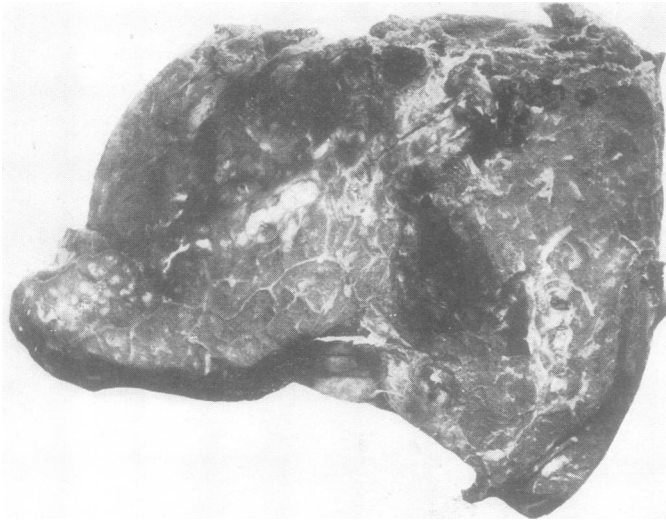

FIG. 11.—Operation specimen from Case 5. Bronchiectasis of the posterior basal branch (right). The anterior branch is filled with laminated exudate and there are areas of collapse distal to this.
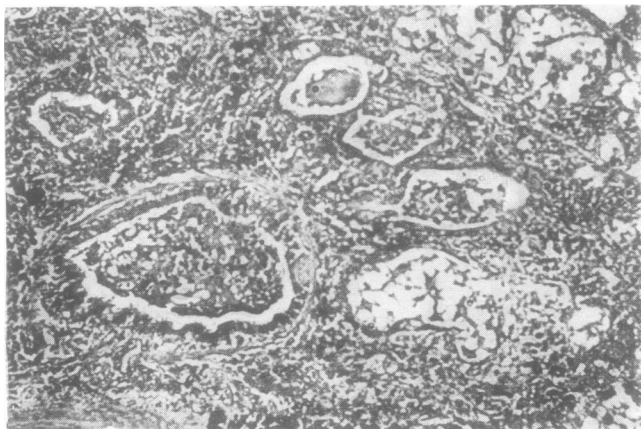

FIG. 12.—Small area of collapse showing crowding of bronchioles which are filled with exudate. (H. and B., × 70.)
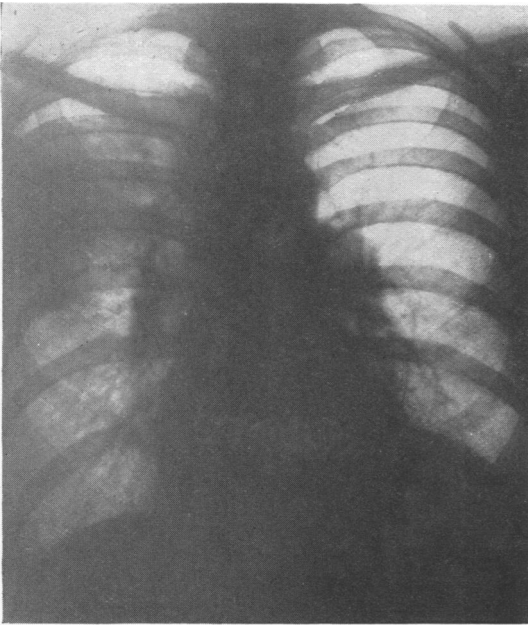
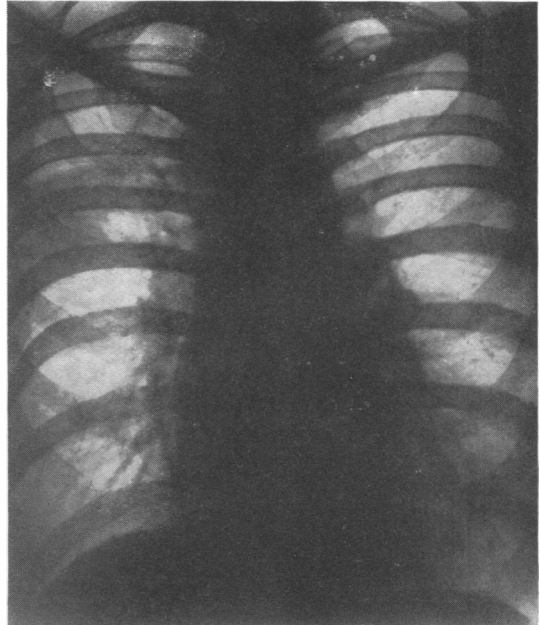FIG. 13.—Case 6: consolidation in the right upper lobe (20.10.47).

FIG. 14.—Case 6: three weeks later the consolidation has almost resolved (12.11.47).

On culture, *A. fumigatus* was identified: subsequently this fungus was repeatedly cultured from the sputum along with other common respiratory organisms. At this time the sputum was observed to contain the plugs which became a characteristic feature of the febrile episodes. Expectoration of the plugs was usually associated with an improvement in her condition and with partial clearing of radiological shadows. She was treated with neoarsphenamine, 0.45 g. intravenously for three doses, and with potassium iodide, 100–150 gr. (7–10 g.) daily for four months, both without effect. She recovered slowly and left hospital in February, 1950. There was a further febrile attack in June, 1950, associated with collapse of the middle lobe; the left lower lobe collapse was still present (Fig. 18).

Bronchoscopically it was confirmed that the fungus was in the middle lobe as well as in the left lower lobe bronchi.

In September, 1950, she was given a course of the diamidine compound, M & B 938, by inhalation, 200 mg. daily in divided doses. Although the left lower lobe started to re-expand at this time (Figs. 19 and 20), it is probable that the drug had little effect on the course of the illness. In January, 1951, consolidation in the right upper lobe was observed during another febrile illness (Figs. 21 and 22): she was then given a course of M & B 938 intravenously, 150 mg. daily for eight days, and during the following month her general condition improved, many large plugs were expectorated, and the right upper lobe cleared. After this *A. fumigatus* was found in the sputum only with difficulty. Again it

is difficult to say whether the drug had any appreciable effect on the course of the illness.

Between April, 1951, and January, 1952, there were several minor febrile episodes; radiographs showed small changing shadows, and the sputum usually contained *A. fumigatus*. Bronchograms in July, 1951, demonstrated saccular bronchiectasis in the right upper lobe, and the middle lobe bronchus filled for the first inch only. The left lower lobe bronchi were crowded and showed slight dilatation.

There was no evidence of disease outside the lungs, and the nasal sinuses appeared normal. Examination of the faeces for ova or parasites, and the blood Wassermann reaction, were negative.

In spite of much illness extending over five years, the patient's general condition remains good, and she is able to lead a fairly normal life between the attacks.

CASE 7.—M. T. E., a woman aged 55 years, had been a schoolmistress for 30 years. Just before her illness she had been using hop manure in her garden, which she said was " flying about all over the place." *A. fumigatus* was found in abundance in the hop manure.

In April, 1951, just after exposure to the hop manure she developed a cough with dyspnoea and wheezing. Because of this she was admitted to a nursing-home in May, 1951, and treated with adrenaline injections. The sputum was purulent and slightly blood-stained. Radiographs showed partial collapse of the left upper lobe. At bronchoscopy a polypoid mass was seen protruding from the left upper orifice; no tissue could be obtained for biopsy. A month later, in July, 1951, she was admitted to hospital with
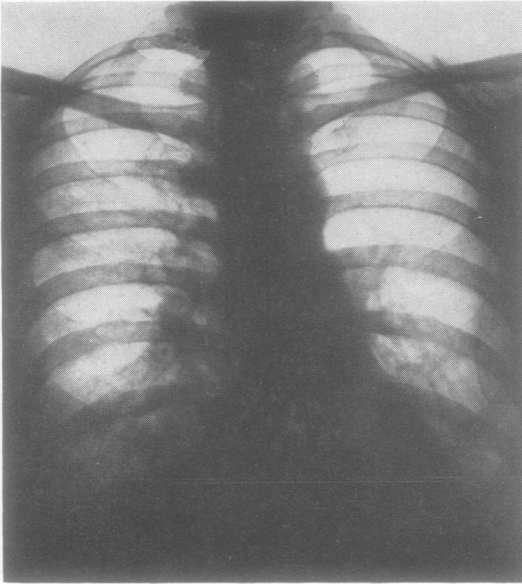
FIG. 15.—Case 6: collapse of the left lower lobe seen behind the heart shadow (13.11.49).

FIG. 16.—Case 6: some re-expansion in the left lower lobe and consolidation in the medial segment of middle lobe (April, 1950).

a provisional diagnosis of bronchial carcinoma. She was pale and thin and her temperature reached 101° F. The collapse of the left upper lobe persisted, and there was in addition partial collapse of the middle lobe (Figs. 23 and 24). The sputum amounted to 2 oz. daily, was purulent, and contained many plugs (see Fig. 2), Charcot-Leyden crystals, Curschmann's spirals, and eosinophils: *A. fumigatus* was grown on culture.
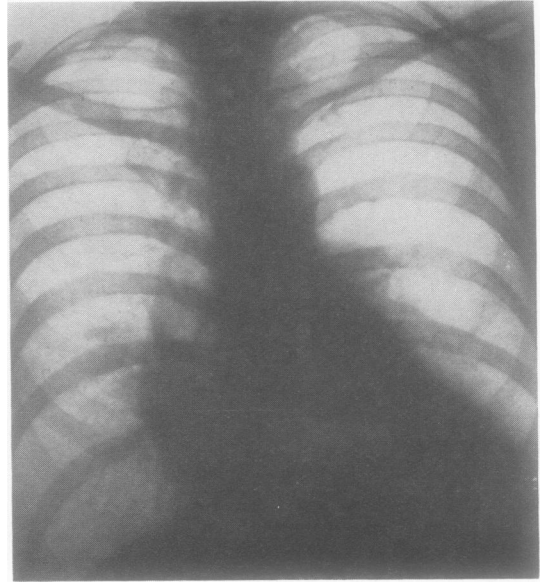
Bronchoscopy was repeated; the left upper lobe orifice was completely blocked by mucopus which was found to contain *A. fumigatus*. No evidence of a polypoid tumour was seen on this occasion. Biopsy from this orifice showed a single septate fungal filament on the epithelium. The middle lobe orifice was clear but exuded mucopus from which *A. fumigatus* was cultured.

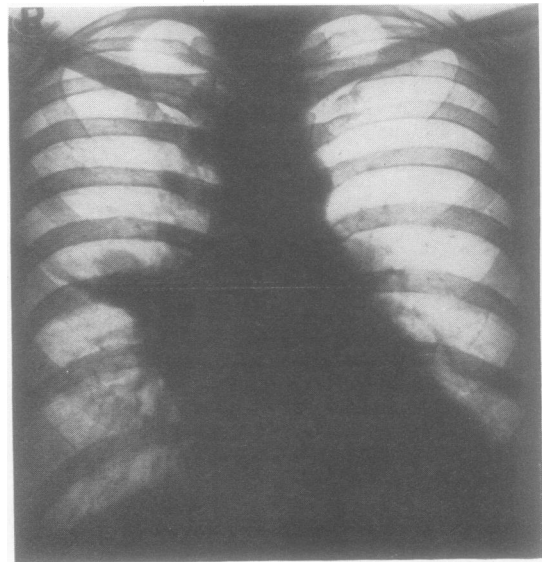FIG. 17.—Case 6: the left lateral view corresponding to Fig. 16 (28.4.50).

FIG. 18.—Case 6: a new shadow in the right upper and middle lobes. The left lower lobe is unchanged (28.6.50).
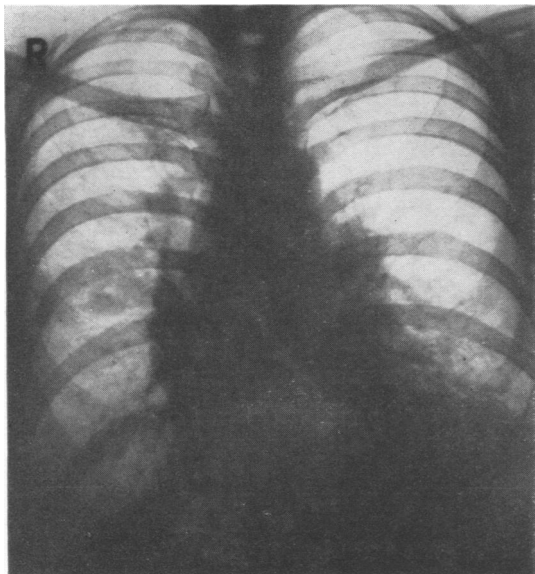
FIG. 19.—Case 6: the left lower lobe re-expanding, some clearing on the right (September, 1950).

ʼFIG. 20.—Case 6: the left lateral view corresponding to Fig. 19 (16.9.50).

Several blood counts showed an eosinophilia of more than 2,000 per c.mm. She was treated by rest in bed, postural drainage, and various sulphonamides. After two months the left upper lobe re-expanded and became almost clear. In October, 1951, there was consolidation of the middle lobe and of a small part of the left lower lobe. The patient was expectorating about 2 oz. (60 ml.) of purulent sputum which contained *A. fumigatus.* On one occasion she
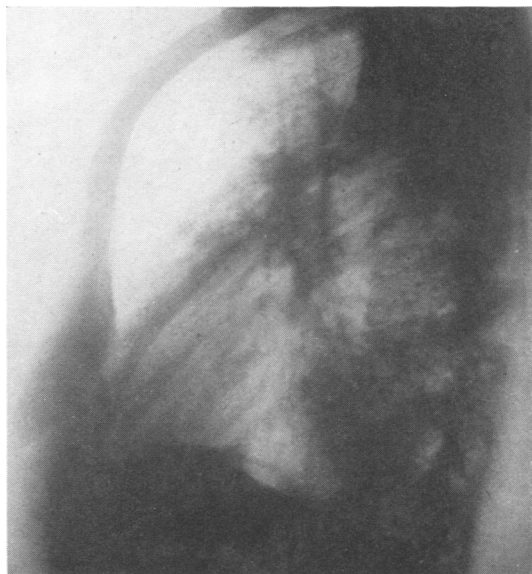
coughed up a bronchial cast which was seen to have many filaments of the fungus embedded in it.

CASE 8.—L. C. D., a man aged 37 years, was a forester but had previously worked in a flour mill.

In March, 1947, he developed bronchitis, and the radiograph showed a small shadow in the left middle zone which cleared rapidly. In January, 1948, there was slight mottling in the right upper zone. In
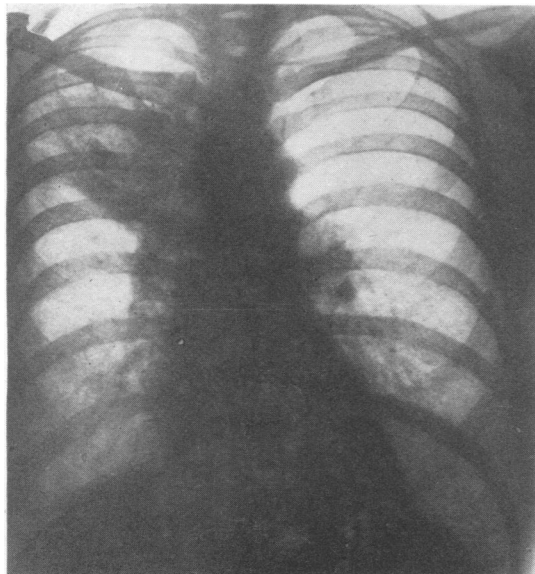

FIG. 21.—Case 6: recurrence of consolidation in the right upper lobe; the left lower lobe not yet clear (15.1.51).
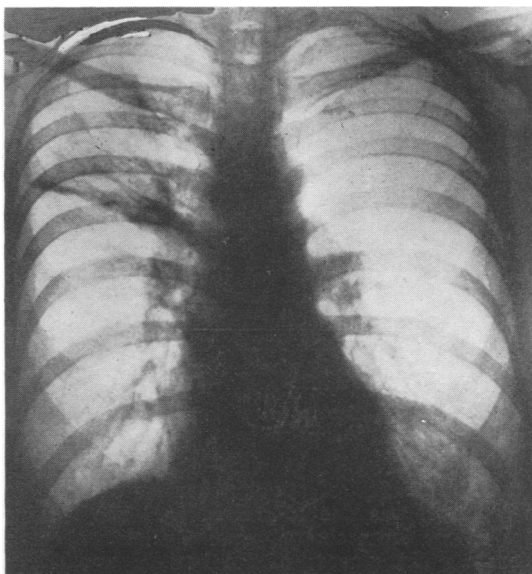

FIG. 22.—Case 6: clearing of the right upper lobe two weeks later (1.2.51).
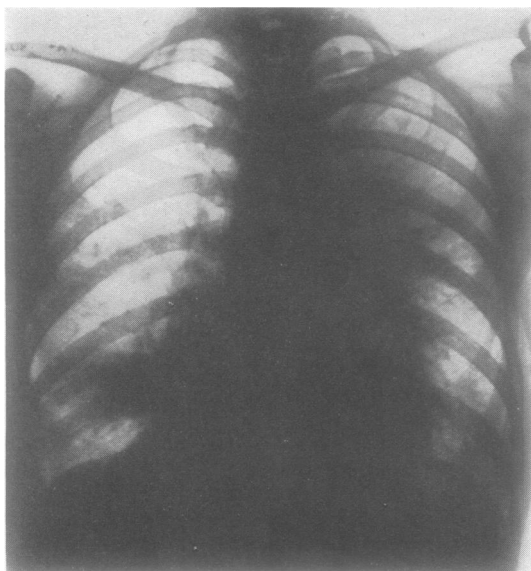
FIG. 23.—Case 7: collapse in the left upper lobe with shadows in the right lower zone (July, 1951).

August, 1949, he developed asthma for the first time in his life: he had a cough and was wheezy, dyspnoeic, and pyrexial. He was admitted to hospital with a diagnosis of pneumonia. A radiograph in September, 1949, showed no change in the right upper zone and a new shadow in the left middle zone. The sputum was purulent and contained *A. fumigatus* and eosinophil cells. The blood eosinophil count was 3,150 per c.mm., and all subsequent counts showed an eosinophilia of more than 1,000 per c.mm. A few weeks later the left middle zone lesion was resolving, but there was a suggestion of middle lobe collapse. A week later this was clearing, but a fresh shadow appeared on the left suggestive of partial collapse and consolidation in the anterior segment of the upper lobe. He was treated with iodides and neoarsphenamine without effect, but improved slowly and left hospital in November, 1949.

In December, 1949, there was another pyrexial attack, and the radiograph showed a left middle zone shadow (Fig. 25). This had largely cleared in two weeks when a new shadow appeared in the right upper lobe (Fig. 26). He recovered slowly after this and remained fairly well until July, 1950, when he experienced his second attack of asthma, and was admitted to hospital, where a radiograph showed mottling in both upper lobes. He died in status asthmaticus the day after admission despite large doses of adrenaline.

Necropsy.—The lungs were distended, and the bronchi were full of sticky, tenacious mucus (Fig. 27). Death was due to suffocation. The cut surface of the lungs showed marked dilatation of the bronchi. The mucosa of the bronchi was thicker than usual, and the bronchi were completely filled with thick, tenacious mucus.

In sections the mucus contained the fungal mycelium with relatively little cellular exudate, except immediately adjacent to the epithelium, where there was a fair number of eosinophils (Fig. 28). The most striking change was the tremendous production of mucus by the cells of the epithelium and the mucus glands. Not only the bronchi but the bronchioles were distended by this material. The fungus itself was seen only in the larger bronchi, and altered blood was not present. It is probable that this intense eosinophilic infiltration and the excessive production of mucus represented an allergic response during the patient's last illness.

OCCUPATIONAL HISTORY

There have been many references to the association of aspergillosis with various occupations which involve the handling of grain, flour, and other vegetable matter (Dieulafoy *et al.*, 1890; Potain, 1891; Rénon, 1893, 1895, 1897; Schneider, 1930; Bethune and Moffatt, 1933; Cannon, 1935; Stolow, 1939; Rubin, 1947; Davidson, 1948; Ungar, 1951).

Coe (1945) reports the only recorded case of compensation being awarded to a man who developed aspergillosis after working in contact with hay, grain, corn, and straw for over 20 years (Legal Case Report, 1942).
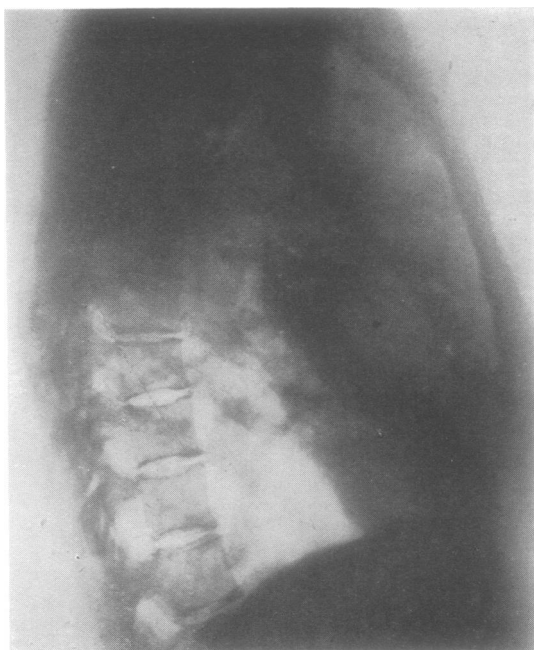

FIG. 24.—Case 7: the right lateral view to confirm partial collapse of the left upper lobe and also collapse with consolidation in the middle lobe (July, 1951).
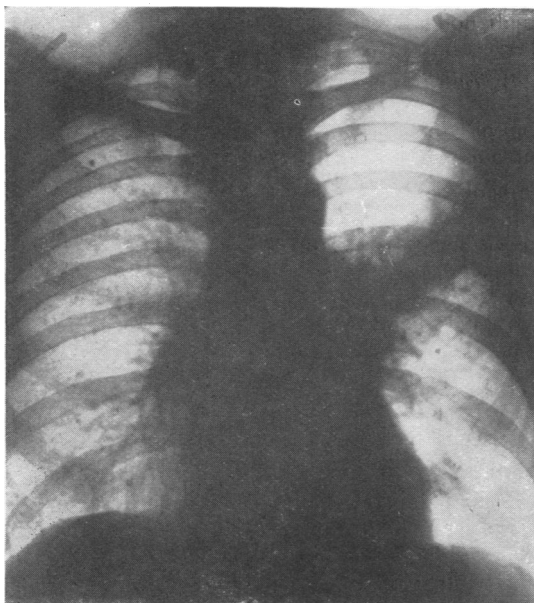
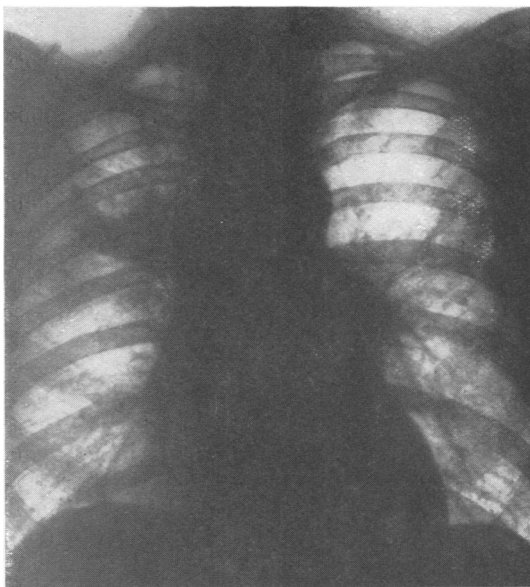FIG. 25.—Case 8: mottling opacity in the left middle zone (7.12.49).

FIG. 26.—Case 8: two weeks later the left mid-zone has largely cleared, but some consolidation has developed in the right upper lobe (21.12.49).

FIG. 27.—Case 8: post-mortem specimen showing widespread bron- chiectasis, with the lumina containing laminated exudate. Pig- mented glands are seen at the centre.

With the exception of Case 5 all our patients had worked in close contact with grain, flour, or other vegetable matter.

CLINICAL MANIFESTATIONS

Aspergillosis, as represented by Cases 1 to 5, which is not associated with an eosinophilia, has often been described in the literature (Rayer, 1842 ; Küchenmeister, 1855 ; Friedreich, 1856 ; Cohnheim, 1865 ; Fürbringer, 1876 ; Lichtheim, 1882 ; Boyce, 1892 ; Holden, 1915 ; Macaigne and Nicaud, 1926 ; Schneider, 1930 ; Peutz, 1932 ; Bethune and Moffatt, 1933 ; Kampmeier and Black, 1934 ; Edwards, 1935 ; Cannon, 1935 ; Norris and Landis, 1938 ; Rodríguez Villegas and Schena, 1941 ; Donaldson *et al.*, 1942 ; Gerstl *et al.*, 1948 ; Heppleston and Gloyne, 1949 ; Ross, 1951). We propose to confine our further discussion of the clinical picture to that type which is illustrated by Cases 6, 7, and 8.

SYMPTOMATOLOGY.—These three patients had pyrexial attacks over months or years with vary- ing intervals between them. In one patient the fever subsided after penicillin therapy although *in vitro* the fungus was not sensitive to it: this suggested that the improvement was due to the elimination of secondary infection. The pyrexial attacks were associated with severe cough and purulent sputum. Staining of the sputum with blood had been noticed a few times, but haemo- ptysis was not a prominent feature. Two of the
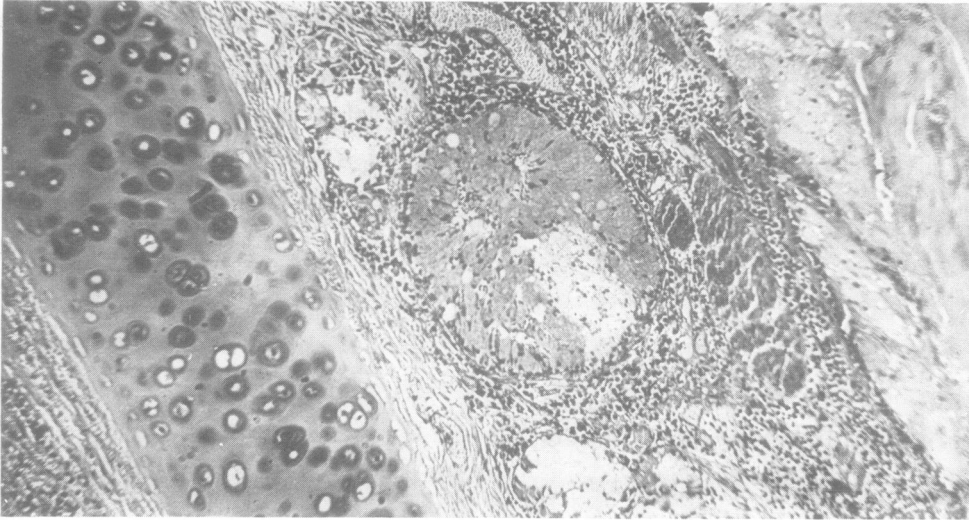
Fig. 28.—Case 8: bronchus (H. and B., × 300). Laminated exudate within the bronchus. Hypersecretion by the mucous glands and eosinophilic exudate in the submucosa.

patients had severe asthmatic attacks, and in the third there were several bouts of wheezing not amounting to true asthma. In the acute episodes there was dyspnoea, and sometimes vague discomfort in the chest but not typical pleural pain.

RADIOLOGICAL FINDINGS.—A single examination is inadequate ; serial radiographs are essential to show the sequence of incidents of lobar or segmental collapse and consolidation, first in one part, then in another and in either lung. These shadows may clear in a week: more often they persist for four to six weeks and sometimes for longer periods. In one case the collapse persisted for nearly a year. Involvement of a new area usually coincides with a pyrexial attack.

SPUTUM.—The sputum produced during the acute episodes is of considerable diagnostic importance. It is always purulent and the fungus will be found if appropriate methods are employed. A particular feature is the presence of the mycelium in white or brownish flecks just visible to the naked eye. In two of our cases these mycelial flecks have been aggregated together with Charcot–Leyden crystals, Curschmann's spirals, mucus, eosinophils, and pus cells into firm, distinctive, rounded masses which are granular, dull, and brownish and measure about a centimetre in diameter. We have called these " plugs " (Fig. 2). They differ from the casts of fibrinous and plastic bronchitis in their colouring, opacity, and shape. After expectoration of one or more of these plugs the patient will sometimes improve both clinically and radiologically, suggesting that a bronchus has " unblocked." On one occasion a bronchial cast containing mycelial threads was expectorated.

The eosinophils, Charcot–Leyden crystals, and Curschmann spirals are found not only in the plugs but also in the sputum generally. *A. fumigatus* may only be found intermittently in the sputum between the acute episodes.

EOSINOPHILIA.—All our cases have shown a persistent eosinophilia of over 1,000 per c.mm.

BRONCHOSCOPY.—Bronchoscopic aspiration will confirm that the organism comes from the affected lobe. Bronchoscopy may also show a polypoid mass obstructing the lumen of a bronchus, leading to collapse and consolidation ; or oedema of the mucosa and a lumen full of tenacious material or mucopus. Subsequent bronchoscopy in two cases showed the polypoid mass to have disappeared although the same bronchus was still infected by the fungus. Bronchial biopsy in one case showed the organism invading the crypts of the mucous glands.

CRITERIA FOR DIAGNOSIS.—Clearly it is insufficient to base a diagnosis of this type of bronchopulmonary aspergillosis solely upon the finding of *A. fumigatus* in the sputum. In our three cases the diagnosis was confirmed histologically, but this is probably too rigid a criterion to demand. We consider that all the characteristic aspects of this variety should be present including recurrent pyrexial attacks, radiological evidence of recurrent collapse and consolidation in different areas, purulent sputum containing " plugs " and the fungus, and a blood eosinophilia of 1,000 per c.mm. or more. Bronchoscopy may offer valuable confirmatory evidence.

Popoff (1887) reported a case showing recurrent chest illnesses in association with asthma and

sputum containing *A. fumigatus*. Rénon (1897) described a similar clinical picture in the pigeon-crammers of Paris. These two descriptions may represent the earliest accounts of the condition which we report in Cases 6, 7, and 8. Unfortunately, in the absence of radiographs, blood counts, and necropsies, a more definite opinion is not possible.

We have tried skin tests with an extract of the fungus in two of the patients and several controls, but found the results inconstant and unreliable. Further work with other extracts may produce better results.

DIFFERENTIAL DIAGNOSIS

This form of aspergillosis may be confused with pulmonary tuberculosis (Hamman, 1927 ; Cohen, 1950 ; Young and Beaumont, 1950), bronchiectasis complicated by pneumonia, carcinoma of the bronchus, and non-specific suppurative pneumonia (Nicholson, 1950). The blood eosinophilia, the presence of the fungus, plugs, and other features in the sputum, and the serial radiological changes will readily differentiate these conditions.

The main difficulty arises in differentiating broncho-pulmonary aspergillosis from pulmonary eosinophilia, the condition recently described by Crofton, Livingstone, Oswald, and Roberts (1952) and also by Weingarten (1943), Viswanathan (1945), Danaraj (1951), and Westwood and Levin (1951). According to the first authors pulmonary eosinophilia includes all conditions in which pulmonary infiltrations are accompanied by an eosinophilia in the blood of more than 6% after excluding resolving pneumonia, sarcoidosis, .hydatid disease, and lymphadenoma. Cases of polyarteritis nodosa, infection by ascaris, by *Brucella abortus*, and by other organisms, and cases with an allergic diathesis fall within the wide scope of this definition. Our last three cases also fall within this definition, but we consider that they should be distinguished from the general group of pulmonary eosinophilia because of the following points of difference: —(1) The plugs we describe in the sputum are not recorded in pulmonary eosinophilia. (2) The relation of the clearing of radiological shadows to the production of plugs is not noted in pulmonary eosinophilia. (3) Illness in our patients continues for years, while cases of pulmonary eosinophilia often clear up in less than six months. (4) The bronchoscopic picture as we describe it is not reported in pulmonary eosinophilia where spasm of the bronchi and oedema of the mucosa are seen without obstructing masses. (5) The macroscopic appearance of dilated bronchi filled with laminated exudate has not been described in pulmonary eosinophilia.

TREATMENT

Our case-histories show that we have not so far found any effective form of treatment. On general grounds bed-rest is indicated during the pyrexial episodes, and physiotherapy with postural drainage has been of benefit in dislodging plugs from occluded bronchi: bronchoscopy may bring about the same result. This is largely palliative treatment, and unfortunately the organism has been found to be insensitive to all the sulphonamides and the common antibiotics and their main value has been to eliminate secondary infection. Eventually it was found that *A. fumigatus* was inhibited by M and B 938 in a concentration of 1 in 100,000. This was given, first by inhalation and then intravenously, in Case 6 of our series, but the results were difficult to assess: there was some slight improvement, but this improvement may well have taken place in the ordinary course of events. Further, M and B 938 caused quite severe hypotensive symptoms after it had been given intravenously.

From the migratory nature of these allergic lesions it seems that surgery has no place in its treatment.

Iodides, as frequently recommended in the literature, and neoarsphenamine have been found to be of no value in the two of our cases so treated.

PROGNOSIS

The evidence that we have so far presented suggests that the prognosis for this form of pulmonary aspergillosis is not good.. One of our patients died in status asthmaticus and the other two still have pyrexial attacks and their sputum constantly contains *A. fumigatus*.

DISCUSSION

The question of the existence of a primary form of pulmonary aspergillosis was discussed with considerable vigour at the end of the nineteenth century (Podack, 1895 ; Rénon, 1897), but eventually the French view that aspergillosis might be a primary infection of the lung was conceded.

The relation of our three cases to bronchiectasis is not clear. Saccular bronchiectasis occurred in two of them. A pre-existing bronchiectasis may provide the stagnation and breach of surface necessary for the implantation of the fungus and this site may then act as a source of infection of other normal bronchi by the fungus. Alternatively, the fungus may initiate blockage of a normal bronchus by mucus, with distal secondary infec-

tion ; this could readily cause bronchial dilatation. We have indeed observed such blocking bronchoscopically, but we have not been able to prove this sequence of events. Crofton and others (1952) considered that bronchiectasis probably followed pulmonary eosinophilia as a complication in four of their patients.

It is difficult to understand why this ubiquitous fungus should, in a very few unfortunate individuals, settle in the bronchi and cause such grave disturbances. Although there are no allergic manifestations in the family or personal histories of Cases 6, 7, and 8, the constant findings of a high blood eosinophilia, the character of the sputum, and the histology of the lesions suggest that the disease is caused by sensitization of the host to this fungus. It is noteworthy that in this group of cases the fungus does not occur as a mass. In " mycetomata " and in infarcts the fungus is agglomerated into dense masses, but high blood eosinophilia and excessive production of mucus do not occur. Case 5 has an eosinophil count of 913 per c.mm.; there are none of the recurrent pyrexial attacks associated with radiological collapse and consolidation, but the bronchi (Fig. 11) are filled with similar material and there are small areas of collapse to be seen in the specimen (Fig. 12). This case may lie between the two types in exhibiting only a mild degree of sensitization.

CONCLUSIONS

From our study we conclude that the fungus may grow on any part of the bronchial tree but especially where there is some pre-existing lesion such as bronchiectasis or tuberculosis with stagnation of secretions or haemorrhage. Here it acts as a pure saprophyte and has no clinical significance.

Rarely, when the human host is overwhelmed by pneumonia, carcinomatosis, or some other disease, the fungus apparently invades the tissues, producing multiple mycotic abscesses or granulomata in the lungs and sometimes in other organs. Recently it has been suggested that such superinfection may occur following treatment with antibiotics in large and prolonged dosage (Abbott, Fernando, Gurling, and Meade, 1952). It seems that this clinical picture of invasion of lungs and other organs may occur as a primary manifestation of aspergillosis without underlying disease (Duncan, 1945 ; Cooper, 1946 ; Cawley, 1947 ; Hertzog and others, 1949 ; Grekin, Cawley, and Zheutlin, 1950).

We present new evidence to show that the host may become sensitized to a fungal infection of bronchi which causes such a reaction that secondary pathological changes occur and these may be severe enough to be fatal or cause prolonged illness.

We therefore suggest the following, in increasing order of severity, as a possible classification : —

TYPE I : SAPROPHYTIC.—This is illustrated by Cases 1, 2, 3, and 4 and possibly 5, and is the variety in which the aspergillus acts as a saprophyte complicating some pre-existing pulmonary condition such as a bronchiectatic cyst (so-called mycetoma), or an infarct and, according to others, neoplasm, tuberculosis, pneumonia, lung abscess, and bronchitis. As a terminal event in such cases this saprophyte may invade the lung tissues.

TYPE II : ALLERGIC.—This is illustrated by Cases 6, 7, and 8, and is that in which sensitization to the fungus leads to the production of an exudate in the bronchial lumen consisting of the mycelium together with mucus, fibrin, eosinophils, Curschmann's spirals, and Charcot–Leyden crystals. This mass leads to bronchial blockage and subsequent collapse or consolidation. There is a high blood eosinophilia and there may be asthma.

TYPE III : SEPTICAEMIC OR PYAEMIC.—This is the variety in which multiple mycotic abscesses or granulomata occur in the lungs and sometimes elsewhere, and has been reported more often in children than in adults. It represents the most serious form of aspergillosis. We have not seen an example of this type. The diagnosis might be suspected when the fungus is present in the sputum and a radiograph of the chest shows miliary mottling in a seriously ill patient.

SUMMARY

The literature concerning pulmonary aspergillosis is reviewed.

An effective method of demonstrating aspergillus in histological preparations is described.

Eight cases of broncho-pulmonary aspergillosis are described, including three (Cases 6, 7, and 8) of a variety not previously recognized. In these three cases there were recurrent pyrexial attacks with radiographic evidence of collapse and consolidation in different parts of the lungs, purulent sputum containing characteristic " plugs " and A. fumigatus, and a blood eosinophil count above 1,000 per c.mm. This type of broncho-pulmonary aspergillosis is thought to be caused by sensitization of the host to the fungus.

A classification is proposed dividing bronchopulmonary aspergillosis into three types: saprophytic, allergic, and septicaemic or pyaemic.

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